Histological Findings in Ruptured Aneurysms Treated with GDCs: Six Examples at Varying Times after Treatment

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Friday, May 17, 2013
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American Journal of Neuroradiology

Key Terms: Background

- **Aneurysm**: localized bulge or “ballooning” in the wall of a blood vessel. The aneurysm can increase in size and rupture that can cause hemorrhage, (rapid outflow of blood) and even death.

- **Guglielmi Detachable Coil (GDC)**: platinum coil used in non-invasive procedures for the occlusion of an aneurysm.

- **Embolization**: selective occlusion of blood vessels by purposely introducing emboli, a form of detached intravascular masses.

- **Arthrosclerosis**: build up of plaque on the inside of blood vessels, which limits blood flow.
Background: Aneurysms and GDC

- Causes of Aneurysms:
  - Congenital, resulting from an inborn abnormality in an artery wall, connective tissue disorders, or circulatory diseases
  - Trauma or injury to the head, high blood pressure, infection, tumors, atherosclerosis
  - Smoking cigarettes, drug use, and oral contraceptives

- Treatment of Aneurysms:
  - Microvascular clipping
  - Endovascular embolization (Guglielmi Detachable Coil)
  - Embolization with retrievable platinum coils

Aneurysm Formation

http://upload.wikimedia.org/wikipedia/commons/8/80/Cerebral_aneurysm_NIH.jpg
Discussion Question

Given the definition and components of GDC, why do you think this design, material, etc. was used for the purpose of treating aneurysms?
Background: GDC Procedure

http://www.theuniversityhospital.com/stroke/hemorrhagic.htm

Aneurysms Treated with GDCs
Background: Problems with GDC

- Inflammatory changes and scar formation within the aneurysm occur over time
- GDC surgeries often result in the adverse effect of acutely ruptured aneurysms

http://www.mayfieldclinic.com/PE-AneurRupt.htm
Purpose

• Show how time affects the coils embedded in the aneurysm, its neck, or its walls

• Histologically evaluate the inflammatory changes and scar formation that occur over time in acutely ruptured aneurysms after GDC treatment
Key Terms: Methods

- **Subarachnoid Hemorrhage**: a dangerous condition in which blood collects beneath the arachnoid mater, a membrane that covers the brain that can lead to strokes, seizures, and brain damage.

- **Basal Leptomeninges**: composed of the two innermost layers of tissue that cover the brain and spinal cord, including the arachnoid matter.

- **Cerebral Arterial Circulus**: a ring of arteries at the base of the brain.

- **Hess and Hunt Scale (H&H)**: a grading system used to classify the severity of a subarachnoid hemorrhage based on the patient's clinical condition. Higher grade correlating to lower survival rate.
Methods: Preparation of the Aneurysms

- Nov 1992-Feb 1999: 247 patients with intracerebral aneurysms were treated with GDCs
- Problems:
  - Lack of consent from relatives
  - Patient transferred before they died
  - Autopsies and dissections limited in value
  - Aneurysm structure and position of coil destroyed by the incision scalpel
Methods: Preparation of the Aneurysms

• New method used, similar to preparations for thin bone sections
• Autopsies performed on six patients with acute subarachnoid hemorrhage
• Aneurysm rebleeding was not the cause of death in any case
Methods: Preparation of the Aneurysms

- Brains were fixed in 10% formalin for 2 to 3 weeks
- The innermost layers of tissue and arteries at the base of the brain were removed
- Aneurysms cleansed, dehydrated in petroleum and gasoline, then submerged in plastic
Methods: Preparation of the Aneurysms

- 2mm slices were taken perpendicular to the orifice of the aneurysm, or where the opening to the aneurysm is, and applied to a glass slide
- The slices were further processed by a grinding machine for the bottom surface and the top surface grounded to a thickness of 5 to 10 µm
- 250 µm thick sections were also prepared (Fig 1)
Discussion Question

What are some advantages and disadvantages of using thin sections of the aneurysm and platinum coils embedded in plastic?
Methods: Preparation of the Aneurysms

- Each slide was stained with toluidine blue and embedded in Eukitt (mounting medium)
Methods: Case Selection

3 Cases:
- Death 5 days after treatment
- Death 113 days after treatment
- Death 272 days after treatment
Methods: Case Selection

• The clinical course of any patient was not considered. Only the effect of coiling at different time points.
Discussion Question

“An examination of the clinical course of any of the patients was not the subject of the present study; rather the effect of coiling at different points of time was studied.”

Explain what kind of variable would be introduced by including the direct medical treatment of the patients.
## Patients, aneurysms, and clinical characteristics in six autopsied cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age at Time of Death</th>
<th>H&amp;H</th>
<th>Aneurysm Size</th>
<th>Time Lapse (days)</th>
<th>Aneurysm Location</th>
<th>Cause of Death</th>
<th>Survival (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>M</td>
<td>43</td>
<td>III</td>
<td>l</td>
<td>1</td>
<td>Medial cerebral artery</td>
<td>Brain swelling</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>41</td>
<td>III</td>
<td>m</td>
<td>1</td>
<td>Superior cerebellar artery</td>
<td>Brain swelling</td>
<td>12</td>
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<tr>
<td>3*</td>
<td>F</td>
<td>48</td>
<td>IV</td>
<td>m</td>
<td>2</td>
<td>Anterior communicating artery</td>
<td>Brain swelling</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>58</td>
<td>III</td>
<td>s</td>
<td>1</td>
<td>Anterior communicating artery</td>
<td>Vasospasm</td>
<td>20</td>
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<tr>
<td>5</td>
<td>F</td>
<td>43</td>
<td>IV</td>
<td>m</td>
<td>1</td>
<td>Basilary tip</td>
<td>Brain swelling</td>
<td>26</td>
</tr>
<tr>
<td>6*</td>
<td>F</td>
<td>72</td>
<td>V</td>
<td>m</td>
<td>1</td>
<td>Basilary tip</td>
<td>Frontal cerebral bleeding</td>
<td>272</td>
</tr>
</tbody>
</table>

Note.—H&H indicates Hunt and Hess Scale grade at admission; *, case discussed in present text; m, male; f, female; l, large (>15 mm); m, medium (6–15 mm); s, small (<6 mm). Time lapse is number of days between first bleeding and treatment; survival is number of days survived after treatment.
Key Terms: Results

- Cerebellar herniation: high intracranial pressure that occurs when a part of the brain is squeezed across structures in the skull.
- Edematous tissue: swollen tissue.
- Infarction: an area of tissue that undergoes necrosis as a result of obstruction of local blood supply, as by a thrombus or embolus.
- Ischemia: a decrease in blood supply to a tissue due to obstruction of blood vessels.
- Siderosis: chronic inflammation of the lungs due to inhalation of iron particles.
- Angiogram: medical imaging technique used to visualize the inside, or lumen, of blood vessels; done by injecting a radio-opaque contrast agent into the blood vessel and imaging using X-ray based techniques.
Results: Case 1

- Days after GDC treatment: 5
- Extensive thrombosis in right leg.
- Sudden and severe thrombosis in pulmonary arteries.
- Cause of death – Edema (swelling caused by fluid) and hemorrhaging (bleeding) throughout parts of brain.

Aneurysm
- Location: Medial Cerebral Artery
- Size: 10x5x5 mm (Large)
- Wall: Connective tissue 140-600um thick
- Coils: loosely filled cavity, none in neck or artery lumen

- Aneurysm cavity blocked with thrombus of RBCs and fibrin with macrophages between clot and artery wall
Results: Day 5 Histology

- Visible thrombus consisting of fibrin and erythrocytes
Results: Case 2

- Days after GDC treatment: 12
- Severe hemorrhaging throughout brain stem.
- Cerebral arteries were sclerotic with nests of macrophages
- Cause of death – Edema and severe tissue death in many parts of brain.

Aneurysm
- Location: Superior Cerebral Artery
- Size: 8 mm in diameter (Medium)
- Neck size: 1.3mm diameter
- Wall: Colagenous tissue 220-640um thick
- Coils: Few coils against walls of aneurysm, none going through the walls

- Aneurysm cavity was partially filled with unorganized and foamy macrophages
Results: Case 3

- Days after GDC treatment: 13
- Eosinophilic neurons in cortex
- Cause of death – Massive edema and severe bleeding near brain stem
- Aneurysm
  - Location: Anterior communicating artery
  - Size: 5 mm in diameter (Medium)
  - Neck size: 1.2mm diameter
  - Wall: Colagenous tissue 250-600um thick
  - Coils: Partially filled cavity forming basket shapes on the walls
- Aneurysm was completely occupied by thrombus extending into the arterial lumen and was covered by cells resembling endothelium
Results: Day 13 Histology

- Endothelium-like cells appear
- Foamy giant cells between coils
Results: Case 4

- Days after GDC treatment: 20
- Extensive edema and hemorrhaging especially near base
- Recent necrosis of cerebral arteries and cerebellum with macrophage invasion
- Cause of death – Recurrent vasospasms resulting in dead cerebral tissue
- Aneurysm
  - Location: Anterior communicating artery
  - Size: 4 mm in diameter (Small)
  - Wall: Connective tissue 50-275um thick
  - Coils: Only a few found near the walls
- Fibrocytes and macrophages present with fresh coagulation and proliferating nearby arteries at >50% of vascular lumen.
Results: Case 5

- Days after GDC treatment: 26
- Extensive dead tissue and necrosis found from 1 day to 3 weeks old
- One area of old necrosis
- Cause of death – Massive brain edema swelling and central hemorrhage
- Aneurysm
  - Location: Top of basilar artery
  - Size: 5 mm in diameter (Medium)
  - Wall: Thin walls only 7-80um thick
  - Coils: Only a few found in aneurysm
- Most of lumen filled with fresh clot and no degenerative changes or thrombosis found in basil artery.
Results: Case 6

- Days after GDC treatment: 272
- Old hemorrhage on ventral part of brain stem
- Different stages of hemorrhaged tissue found throughout
- Cause of death – Massive recurrent cerebral hypertensive hemorrhage that separated midline structures
- Aneurysm
  - Location: Between basilar artery and posterior cerebral arteries
  - Size: 8 mm in diameter (Medium)
  - Neck size: 4mm diameter
  - Wall: Thin walls only 60-400um thick
  - Coils: No coils reaching out neck into blood vessel
- Large multinucleated giant cells found adjacent to coils and orifice completely covered by thin layer of cells resembling endothelium
Results: Day 272 Histology

- Scar-like tissue in aneurysm lumen
- Vascular connective tissue around coils
- Giant cells with multiple nuclei around coils
Discussion

- Analysis of body’s time-dependent, cellular response to GDCs in treating aneurysms

Discussion Question: How do the three cases chosen to analyze in this work (5, 13, and 272 days after treatment) and their findings correspond to what we know about the wound healing response to an implant?
Discussion: Wound Healing

- injury (in this case implantation)
- coagulation – (day 5) within the first few days after injury/implantation
- inflammation – (day 13) immediately following coagulation phase
- repair and remodeling – (day 272) continual process over a long period of time
Discussion: 1) Implantation

- after GDC treatment of an aneurysm, blood pulsation is reduced
- limit of blood flow allows for coagulation response and clotting
Discussion: 2) Coagulation

- represented by case 1, 5 days post treatment
- Findings:
  - thromboembolized clot with erythrocytes and fibrin between coils and within lumen
  - Indicative of coagulation phase in healing process

- Fig 1D: thrombus with fibrin and erythrocytes; Fig 1E: single macrophage
Discussion: 3) Inflammation

- represented by case 3, 13 days post treatment
- Findings:
  - foamy macrophages present between coils
  - Indicative of inflammation cascade
  - macrophages for phagocytosis in response to foreign body/particles

- Fig 3E: foamy giant cells found between coils
Discussion: 4) Repair and Remodeling

- represented by case 6, 272 days after treatment
- Findings:
  - scar tissue, connective tissue, and endothelial cells form throughout the wound healing process
  - caused by:
    - pressure placed on coils translated to aneurysm wall
    - reaction of the wall to the foreign body

- Fig 4D: vascularized connective tissue around coils; Fig 4F: scar tissue mimicking endothelial cells, found at border of aneurysm and vessel
Discussion: Factors influencing tissue development

• formation of vascularized connective tissue and endothelial cells at the neck of the aneurysm are favorable results

• type and location of tissue formation is dependent on the aneurysm, coil location, and attenuation/density of the coil mesh

• 2 Factors:
  – Neck width in relation to aneurysm volume
  – Coil migration
Discussion Question

Describe how you believe the diameter of the neck of the aneurysm in proportion to its volume would affect the healing response of the aneurysm?
Discussion: Aneurysm Neck Width

- wider neck in proportion to volume is LESS likely to contain enough coils for adequate mesh within the aneurysm
- cause less developed mesh
Discussion Question

• coils within the vessel lumen can impact flow conditions
• coils in a liquid or semi-liquid move
• in a low attenuation mesh, this will highly influence coil movement

Why would coil migration be detrimental to eliminating an aneurysm?
Discussion: Coil Migration

• With inadequate mesh:
  – blood pulsation will play a greater role on inner aneurysm coils if the mesh is poorly formed, impacting tissue development
  – can cause: aneurysm recanalization, no macrophage movement, no scar tissue formation, movement of blood clot

• With adequate mesh:
  – water hammer effect (pressure wave due to redirection of flow) causes movement of coils and then settling
  – can still have normal scar tissue and endothelial development